THE PLASMA PROTEINS IN RELATION TO BLOOD HYDRATION

IX. Serum Proteins in the Terminal Stages of Renal Disease

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The three preceding papers of this series (1, 2, 3) have dealt with the concentration of serum proteins in chronic edematous nephritis, acute nephritis and heart failure, respectively. It has been shown that in all these conditions serum albumin deficiency is common and is related to edema production. However, the correlation between edema and albumin deficiency is exact only in chronic edematous nephritis, in which circulatory and vascular disturbances are minimal. In all three diseases, hypoalbuminemia, irrespective of its relation to edema, appears to be due chiefly to malnutrition,—or, more exactly, protein deprivation,—which may be referable partly to proteinuria, but is usually chiefly the result of inadequate protein intake.

The present paper deals with the serum proteins in the terminal stages of renal disease. Total proteins have been determined 266 times on 61 cases; protein fractions 81 times on 24 cases. In 130 instances in 42 cases blood cell volume was determined by means of a Daland hematocrit, and oxygen capacity by the method of Van Slyke and Stadie (4) or that of Van Slyke and Hiller (5). On 35 additional occasions, in 13 cases, either oxygen capacity or cell volume was determined. In 1 case the volume of the circulating plasma was determined by the vital red method of Keith, Rowntree and Geraghty (6).

The cases can be divided roughly into 3 groups: 1—chronic glomerular nephritis; 2—arteriosclerotic nephritis, and 3—patients with destructive lesions of the kidney. The last group, which will, for convenience, be designated as "suppurative nephritis," includes patients with bilateral pyonephrosis or pyelonephritis, bilateral renal tuberculosis, and polycystic kidneys. The nature of the underlying disease has no demonstrable effect on the serum proteins, which appear to be influenced only by the functional disturbances to which the disease gives rise. Most of the patients were studied over relatively short periods in the last stages of renal disease. A few were observed at earlier stages, some for periods

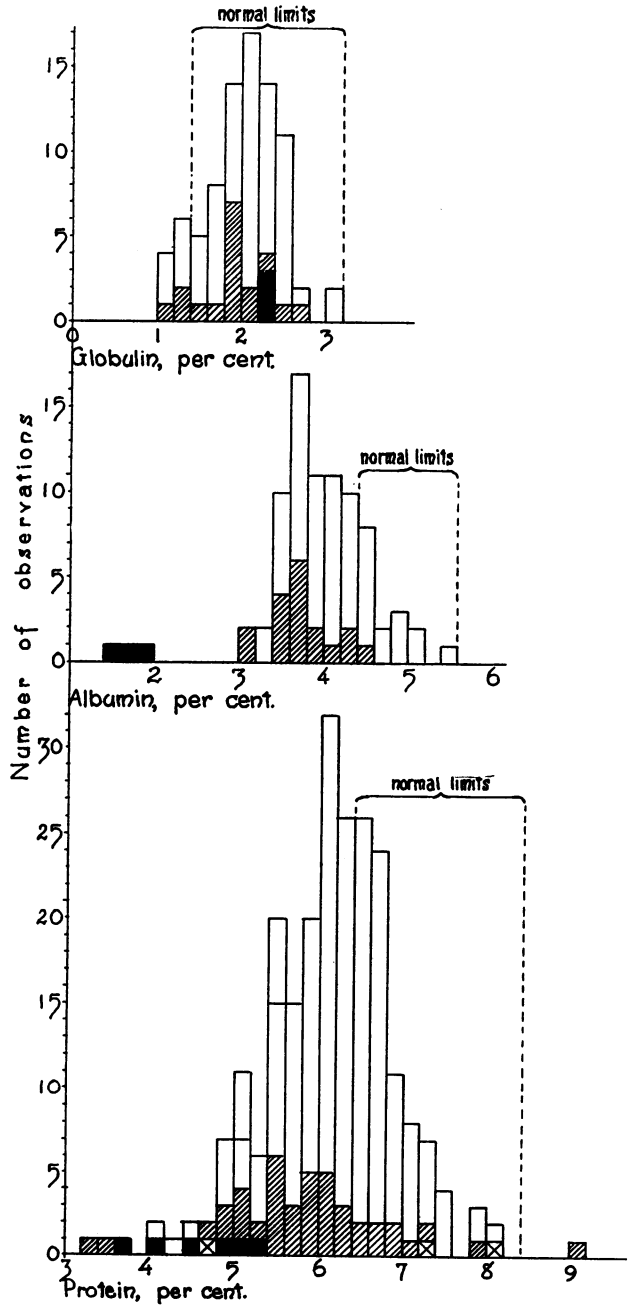

FIG. 1. THE RELATION OF SERUM PROTEINS TO EDEMA IN TERMINAL NEPHRITIS.

Solid squares represent edema without heart failure; diagonally lined squares, edema with heart failure. The squares with crosses are from a single case with dermatitis exfoliativa due to luminal poisoning.

of as much as 2 or 3 years. All exhibited evidence of impaired kidney function in inability to concentrate urine; most had extreme reduction of phenolsulfonephthalein excretion and high blood nonprotein nitrogen.

In Figure 1 all the protein data are presented, as they have been in the preceding papers, with especial reference to the incidence of edema. An attempt has been made, however, to distinguish between edema associated with heart failure and edema occurring without evidence of circulatory decompensation. In cases of this type such a distinction is fraught with difficulties and must, in the last analysis, rest upon the judgment of the clinical observer. In the great majority of instances, in this series, in which edema is connected with heart failure, there were unequivocal objective signs of cardiac disease with decompensation. Pericarditis, coronary occlusion, paroxysmal tachycardia, cardiac irregularities, evidence of advanced chronic passive congestion of the lungs and other organs, were the commonest of these signs, especially in the premortal stages of the disease. Dyspnea with cyanosis, but without reduction of the alkaline reserve or obvious pulmonary pathology, was considered a sufficient indication of heart failure, as was response to digitalis by clinical improvement and diuresis.

In far more than half the observations serum protein was distinctly below the normal level, with occasional deficits quite as great as those encountered in nephrosis. As in the other conditions which have been studied it is entirely the albumin fraction of the serum which suffers, globulin remaining relatively unaltered. These observations agree with those of previous observers (7, 8, 9).

At first sight there appears to be no semblance of correlation between the protein level and the incidence of edema. In fact the single patient with proteins distinctly above the normal range had general anasarca. On closer examination it becomes evident that edema is both relatively and absolutely more frequent when the proteins are reduced. What is more significant is the fact that edema without signs of heart failure is found only when there is a definite serum protein deficiency.

In the production of the hypoalbuminemia, proteinuria may play a part, at times not negligible. However, in some of the cases with greatly reduced serum albumin proteinuria has been quite insignificant. Abnormally large serum volume due to hemodilution can be excluded because the globulin is not reduced. Moreover, direct determinations of serum volume by the dye method made by Brown and Rowntree (10) revealed no tendency to hemodilution in cases of this type. As will be shown subsequently hemoconcentration is probably a far commoner occurrence.

In Figure 2 an attempt has been made to compare the serum protein concentration with the state of nutrition of the patients. The criteria which have been employed in the evaluation of the nutritive state have been discussed at length in the preceding papers (6, 7, 8). They are,

obvious emaciation, evidence of recent large weight losses and, in a few instances, records of subsistence over long periods on inadequate diets. In addition, it has been necessary to give especial consideration to vomiting, which is, in this condition, so common and so serious a symptom. In the figure, vomiting cases are distinguished from those with malnutrition due to other causes. Occasional vomiting has not been recognized, but only vomiting of such frequency, severity and duration as to prevent the oral administration of reasonable amounts of food and fluids, and to produce dehydration.

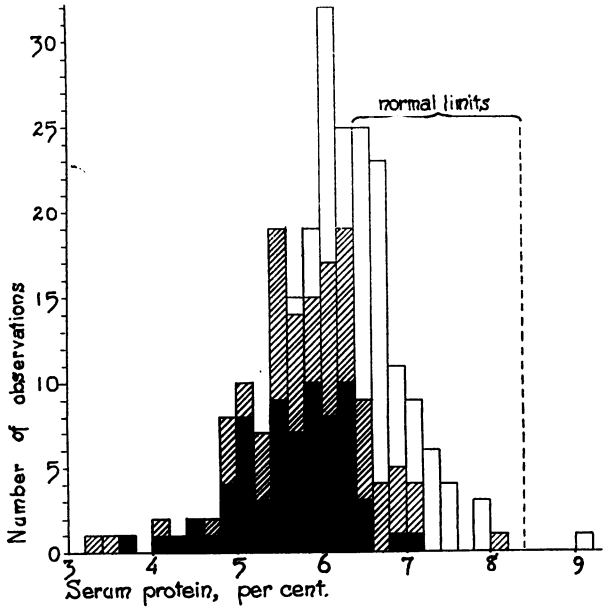

FIG. 2. THE RELATION OF SERUM PROTEIN TO MALNUTRITION IN TERMINAL NEPHRITIS.

Solid squares represent malnutrition; diagonally lined squares, persistent vomiting.

If the vomiting cases are added to those with malnutrition due to other causes, there can be no reasonable doubt that chronic nephritis is a wasting disease. Vomiting alone is noticeably more frequent at high protein levels, malnutrition from other causes at low protein levels. This trend can be reasonably ascribed to the dehydrating effects of emesis. This explanation, furthermore, finds support in the records of individual patients who have been studied before and after vomiting began and others in whom vomiting has ceased or its effects have been overcome by the parenteral administration of fluids. In such cases more or less parallel fluctuations of serum protein, cell volume and oxygen capacity are seen.

Even if the vomiting cases be omitted there is a surprisingly large incidence of severe malnutrition with little or no protein deficiency, which can be explained only by consideration of the serum proteins in individual cases. The hemoconcentration which may result from heart failure, especially when fluids are restricted, has been discussed in the preceding paper. In that discussion one of the cases in this series, the one with proteins above the normal range in Figure 1, was mentioned. An opportunity to observe the phenomenon more exactly and frequently was presented by a group of patients with nephritis who developed acute heart failure as a terminal condition. Under these circumstances certain changes in the constitution of the blood occurred with great regularity. The serum proteins rose sharply, while blood cell volume and oxygen capacity remained unaltered or diminished. Examples of this association of events are shown in the first two cases in Table 1. In 7 of the 11 cases in which studies were made before and after sudden heart failure the serum proteins rose, the increases varying from 0.31 to 1.52 per cent. In one case they remained unchanged. In the three cases in which they fell large quantities of fluid had been given subcutaneously or intravenously shortly before the observations were made. Oxygen capacity fell in 7 out of 8 instances, in the other remaining unchanged. Cell volume fell in 7 instances, rose once and remained unchanged once. The simplest explanation for the protein increase is passage of fluid without proteins from the blood to the tissue spaces. The simultaneous reductions of cell volume and hemoglobin can hardly be due to blood cell destruction; but are probably a result of circulatory stagnation, which causes cells to become segregated in certain parts of the circulation. This concentration of the serum in heart failure accounts for a certain number of the observations in which the proteins are high in malnourished patients who were not vomiting.

Attention has been called, in another connection (11, 12), to the impairment, in advanced nephritis, of the mechanisms by which the salt and water content of the body is usually stabilized. If the salt intake of the patient with severe renal damage is restricted, dehydration results because urinary salt excretion does not diminish to the same extent that it does in normals. Restriction of fluids also leads to dehydration because of the tendency to diuresis, the polyuria of renal insufficiency. With dehydration from these causes hemoconcentration usually occurs. Alterations of serum proteins associated with variations in salt and water intake are illustrated in the third and fourth cases in Table 1.

Although there is a tendency, in individual cases, especially over short periods, for hemoglobin, cell volume and serum proteins to vary together, there is no demonstrable general correlation between serum proteins and either cell volume or hemoglobin. Profound anemia may be found in advanced nephritis without serious protein deficiency, and

TABLE 1

Data concerning blood, edema, and weight

Case number	Date	Blood non-protein nitrogen	Weight	Serum proteins	Blood		Edema	Remarks
					Cell volume	Oxygen capacity		
		mgm. per 100 cc.	*kilos*	*per cent*	*per cent*	*volumes per cent*		
22684	December 13	105	61.8	7.07	28.2	12.9	0	Malnourished and dehydrated from continuous vomiting
	December 19	105	60.4	6.75	23.5	9.8	0	Still eating little, but taking fluids better
	December 31	178		7.06	21.2	9.5	0	Coronary occlusion on December 26. Death January 1
29039	January 25	233		5.82	12.0	4.3	+	Extreme emaciation, dehydration and vomiting
	January 26	253		3.41	11.1	4.4	2+	After large amounts of fluid subcutaneously
	January 27	254		3.30	10.6	3.8	2+	Parenteral fluids continued
	January 28	254		5.60	10.4	3.8	2+	Pericarditis and acute heart failure appeared June 27. Death January 29
26409	November 20	42	54.8	6.89	42.8	17.8	0	Undernourished and vomiting steadily
	November 28	39	53.4	7.23	39.1	17.3	0	After salt poor, high fluid treatment
	December 5	41	52.8	6.34	36.7	16.4	0	After limited fluids with 7 grams NaCl daily
	December 17	47	50.0	6.63	38.5	16.9	0	After salt poor, high fluid treatment
	December 27 1924	81		5.74	35.5	16.2	0	2 days before death. Extremely emaciated
29267	February 19	85	67.9	6.66	29.4	14.8	0	No heart failure nor vomiting
	February 25	75	66.4	7.09	32.6	15.0	0	After a salt poor diet
	February 29	69	66.1	6.74	32.5	14.3	0	After restricted fluids with 5 grams of NaCl daily
	March 8 1925	44	68.2	6.27	31.3	13.8	0	After high fluids with 5 grams of NaCl daily
	January 14	75		6.93		12.7	0	Seen in dispensary
	November 19	167		6.61	23.0	8.7	0	Readmitted, emaciated, dehydrated and vomiting
	November 27	168		6.31	21.3	8.4	0	Taking food and fluids better
	December 1	167		5.09	17.1	7.3	0	Vomiting. Receiving large amounts of fluid and salt subcutaneously
	December 6	163		6.17	17.1	5.9	0	Frequent convulsions. Less fluids given
	December 11	158		5.62	15.3	4.9	0	Improving. Receiving large amounts of fluids
	December 17 1926	145		5.89	20.0	7.4	0	Eating and taking fluids by mouth
	January 2	165		6.49	18.3	7.1	0	Eating well. Taking less fluid
	January 9	171		4.49	14.9	5.1	0	Pericarditis and heart failure. Parenteral fluids. Death January 11

low albumin with little reduction of hemoglobin. Furthermore, peculiar divergences of hemoglobin and proteins are seen in individual cases. An example of such divergence in acute heart failure has already been mentioned. Others have been found which can not be explained so easily. In the second case of Table 1, number 29039, between the first and second observations, within 24 hours, proteins fell 2.4 per cent while hemoglobin and cell volume remained practically unchanged. One can argue with no certainty that the administration of large amounts of fluids, increasing the blood volume, swept cells from stagnant portions of the circulation. In this and the preceding case determinations were made on arterial blood. This is only one instance in which, even during very short periods, the concentrations of the cellular constituents of the blood and of the protein exhibit large and entirely unrelated changes. Numerous other similar occurrences can be found in the Table.

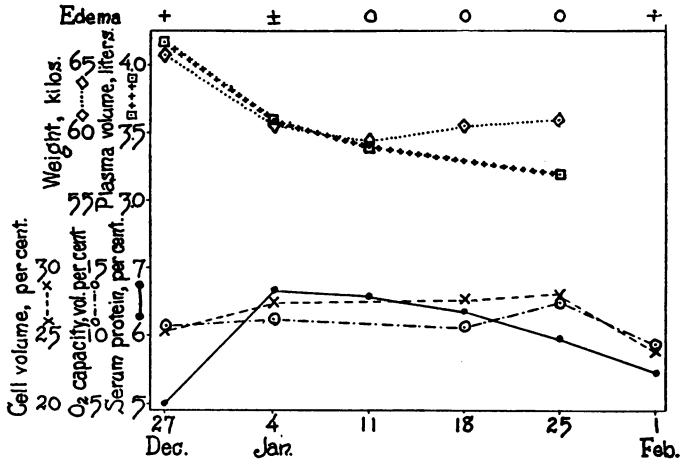

FIG. 3. CHANGES OF SERUM PROTEIN, IN THE TERMINAL STAGE OF NEPHRITIS, COMPARED WITH CHANGES OF SERUM VOLUME AND BLOOD CELL VOLUME. CASE NUMBER 56247.

Figure 3 shows perhaps the most extraordinary example of the lack of relation between proteins and cellular constituents. In this case determinations of serum volume by the vital red method afford a more accurate basis for the analysis of the fluctuations in proteins and cells. The patient, an Italian male, aged 39, was admitted to the hospital December 26, 1926, with advanced chronic nephritis. He appeared well nourished, but had vomited continuously for some days. There was slight edema of the ankles which was ascribed to heart failure and disappeared rapidly with rest and digitalis. Vomiting ceased almost entirely after he entered the hospital, but he was not able to take large amounts of fluid and voided relatively large quantities of urine. There is an immediate rapid drop of weight with a striking reduction of plasma volume and

a simultaneous increase of serum proteins, evidently due to hemoconcentration. This reduction of plasma volume is accompanied, however, by a relatively insignificant rise of hemoglobin and cell volume. At the third observation weight and plasma volume have continued to fall, at a diminished rate. This time the proteins have also decreased. Meanwhile the nitrogen balance has been continuously negative, with losses amounting to about 16 grams of protein daily. From this time until death the serum proteins diminish steadily, the negative nitrogen balance continuing with only a brief interruption. Plasma volume, on the one occasion when it was again determined, had fallen still further, in spite of the administration of large amounts of salt and water.[1] The temporary rise of hemoglobin and cell volume at the next to last observation may be partly referable to a transfusion given on January 19. The gain of weight towards the latter part of the illness probably represents retention of fluid preceding the appearance of demonstrable edema, associated with heart failure. The final fall of hemoglobin and cell volume may be connected with terminal exacerbation of the heart failure. After the fifth observation, January 25, vomiting became so extreme that the patient took no food and received fluids almost entirely by hypodermoclysis or infusion. One is tempted to ascribe the initial rapid rise of serum proteins to hemoconcentration, the subsequent gradual fall to continued malnutrition. Whatever may have been the causes of the changes it is obvious that the reduction of plasma volume tends to mask the true extent of the serum protein depletion. If the total amount of circulating protein is estimated by multiplying, in each instance, the plasma volume by the serum protein concentration, the following values are obtained: December 27, 210 grams; January 4, 240 grams; January 11, 230 grams; January 25, 190 grams.

Not only do the concentrations of serum proteins and the cellular constituents of the blood often run divergent courses; even the relation of cell volume to oxygen capacity shows rapid fluctuations. It has been recognized that changes in the reaction of the blood cause the red blood cells to swell or contract. The causes of these reactions have been elucidated by Hamburger (13), Van Slyke (14) and others. In a disease in which disturbances of acid-base equilibrium are so frequent and profound, alterations of the size of the red blood cells are to be expected. They should, however, be of relatively small magnitude, while in some of the nephritic patients of this series the cell volume changes were extraordinarily large. In Table 1 can be found some examples which can not consistently be connected with variations of CO_2, which was simultaneously determined in each case.

[1] This case has been discussed in another article from this department (12). In spite of the administration subcutaneously of enormous amounts of salt, in the latter part of his course, he exhibited a continuously negative chloride balance. A large part of the chloride was excreted through the bowel.

Although considerable attention has been given to the effect of blood reaction on cell size, the effect of total base concentration has not been considered. If, however, the cell membranes are, as is generally believed, impermeable to bases *in vivo* as they are *in vitro* (15), changes in the base concentration of the plasma, unless immediately mirrored by proportional changes in the base content of the cells, must of necessity be compensated by an exchange of fluid between the two phases. Cell size must change. In nephritis serum base concentration is disturbed almost, if not quite, as frequently as are serum pH and CO_2 (9, 10).

DISCUSSION

Reduction of serum protein at the expense of the albumin fraction, then, occurs with great frequency in the terminal stages of nephritis, and may become quite as great as that found in nephrosis. It can not be correlated with the incidence of edema because the latter, when it occurs in this condition, is usually referable to heart failure. Malnutrition is a characteristic feature of the disease and can be demonstrated in all cases that present hypoalbuminemia. On the other hand, serum albumin is often normal or high when there is evident malnutrition. Reasons for this are found in the tendency of these patients to develop hemoconcentration. Among the causes of hemoconcentration are heart failure, vomiting, anorexia and the inability to conserve the salt and water stores of the body. Extreme and rapid fluctuations of serum protein concentration, blood oxygen capacity and blood cell volume are produced by the interplay of these same functional disturbances, which vary the serum volume, blood cell volume and blood cell distribution. Such fluctuations often mask the true extent of the serum albumin depletion.

CONCLUSIONS

1. Reduction of serum proteins at the expense of the albumin fraction is common in the terminal stages of renal disease.

2. The serum albumin deficiency can not be correlated with the incidence of edema, which is usually referable to heart failure.

3. Wasting is a characteristic feature of the condition and can be correlated with the serum protein deficiency, unless some other functional disturbance has produced hemoconcentration.

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